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Regenerative medicine as a disruptive technology

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ORIGINAL RESEARCH

Regenerative medicine as a disruptive technology: implications for manufacturing & clinical adoption

Geoffrey Banda, Joyce Tait & James Mittra

Although regenerative medicine has been described as a disruptive innovation, there has been little critical enquiry into the nature and location of the disruption. This paper, based on ten cases in the UK, analyses the nature of disruption for allogeneic and autologous therapies in terms of manufacturing, distribution and adoption in clinical settings. We discuss the challenges of dealing with inherent variability in living systems and how this necessitates co-evolution of technologies and innovations. We propose that understanding of the distinction between disruptive and incremental innovation, and of the nature, extent and location of the disruption across sectoral value chains, can help to guide company innovation strategies and government innovation support policies for regenerative medicine, as already proposed for industrial biotechnology.

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INTRODUCTION

Regenerative medicine (RM), which promises to cure disease and respond to currently unmet medical needs [1], is frequently described as a ‘disruptive innovation’ [2,3].

However, there has been little critical enquiry into the nature and location of the disruption, resulting in missed opportunities to shape the innovation ecosystem to make it more supportive of RM therapies.

We have defined disruptive and incremental innovation as follows [4,5].

Disruptive innovation involves discontinuities in innovation pathways, requires new areas of research

and development (R&D), creation of new modes of production and/or new markets. It can lead to sectoral transformations and the displacement of incumbent companies, or the creation of entirely new sectors, all with significant societal and economic benefits. There is often no pre-existing business model on which to build a strategy for disruptive innovation and there may also be a need to create a new value chain, or a new role for the emerging technology in an existing value chain.

Incremental innovation fits well with the current business model of a firm. It generates competitive advantage and contributes to the economy through more efficient use of resources, or elimination of wasteful or environmentally damaging practices, but will not lead to sectoral transformations.

This paper builds on the authors' previous research [1,6,7]; providing new empirical data and analysis to inform our thinking on disruptive innovation and how the concept can be operationalized to deliver a more supportive policy environment [5]. The key to this approach is to attend to the extent of disruption of incumbent company business models, the location of that disruption within specific value chains, and the impact of regulatory and policy choices on the location and extent of disruption. Our case study of RM encompasses both allogeneic and autologous therapies:

Allogeneic therapies are developed by collecting cells from a donor, manipulating them to form a master-cell bank, then using them as starting material to produce multiple therapies administered to large numbers of patients, generating attendant economies of scale.

Autologous therapies are based on collection of cells from a patient, manipulation in the manufacturing environment and re-introduction into the same patient within a clinical setting.

In line with the above definitions, both allogeneic and autologous RM therapies are disruptive of the business models of incumbent small molecule pharmaceutical and bio-pharmaceutical companies [1], in that they require radically different approaches to R & D, manufacturing, distribution and marketing. Autologous therapies, while equally disruptive of pharmaceutical business models, could be regarded as a relatively incremental development for companies involved with organ transplants or for blood transfusion services (BTs), albeit with some disruptive elements, given the nature of the properties of the material being handled.

The approach adopted in this paper contributes to understanding where and to what extent autologous and allogeneic therapies display disruptive or incremental innovation characteristics, based on original case study interviews with organizations involved in RM development in the UK. It builds on our previous research to show how a disruptive/incremental lens can add insights that are valuable in devising policies to support the development of innovative technologies.

BACKGROUND

Although there have been significant advances in scientific knowledge and understanding of RM, commercialization and large-scale production of autologous and allogeneic therapies have remained

challenging. For allogeneic therapies, being developed in large scale, centralized manufacturing facilities [8], disruptive challenges include: the time and effort needed for donor material collection, processing and storage in a bio-bank under current Good Manufacturing Practice (cGMP), followed by further processing to produce therapies for patients; cryopreservation of living material, safe distribution of fragile living materials, ensuring traceability of cells following treatment; and dealing with immunogenicity issues in recipient patients. Many of these factors also apply to autologous therapies being developed in localized manufacturing facilities, with additional challenges related to the personalized nature of the therapy, ruling out economies of scale. The Department of Business, Innovation and Skills (BIS) in 2011 [9] suggested that manufacturing viable living cells for RM requires the development of “new technologies, tools and techniques” and, although considerable progress has been made, for example in manufacturing process development, RM therapy value chains are still a long way from delivering a reliable, profitable route to market [10,11].

Lipsitz *et al.* argued that the new RM-related technologies span manufacturing, distribution systems, shelf life enhancement and automation (especially closed manufacturing systems) [12]. This has led to further calls for advances in manufacturing and bio-processing, because of the non-scalability of existing technologies [9] and the need for skills development in the RM niche-focused areas. Abbasalizadeh *et al.* present a deeper analysis of the scientific, technological, and commercialization challenges

of allogeneic therapies, suggesting that although autologous therapies are safer and often the preferred choice, they do not provide a simple off-the shelf product for clinical use [8]. They also argue that production of autologous therapies is time consuming, skilled labor-intensive and, from an operational perspective, the mechanics of isolating cells and delivering the therapy are problematic for elderly and critically ill patients unable to tolerate biopsies. Lipsitz *et al.* demonstrate that lack of highly skilled labor is caused by current manufacturing process requirements and the costs incurred in training operators, including routine validation of aseptic techniques for operators [12]. Additional issues include the need to independently verify batch record protocols, active working time delays due to suiting up procedures with laboratory garments, and the need for additional staff to facilitate gowning. The calls for ‘closed manufacturing systems’ are based on the need to reduce some of these ‘necessary redundancies’ of current clean room operation procedures for cGMP requirements. Other challenges include lack of value chain integration, technology delivery gaps, and arguably inappropriate or disproportionate governance of innovative technologies [4,6]. Given the disruptive nature of RM, new firm-to-firm linkages are needed to create new value chains and, during early development phases, brokerage is important to create links with stakeholders [6]. These disruptive challenges are not experienced by manufacturers of small molecules and other biologicals and they are important for understanding the unique hurdles RM manufacturers face in assuring cellular product

safety, quality and efficacy, as well as traceability and attendant ethical considerations.

Centralized & locally distributed manufacturing approaches

Harrison *et al.* argue that throughout history there has been a steady shift from localized, decentralized production systems to centralized production systems, underpinned by the need to achieve economies of scale and scope [13]. Centralization was possible where manufacturers were dealing with standardized bulk products, which could be easily characterized and analyzed and were accompanied by increasingly automated processing and quality assurance systems. Lipsitz *et al.* argue that, for RM therapies, scalable production methods will determine the cost of goods sold, leading to the policy focus on allogeneic therapies because of their *potential* economies of scale and investment palatability making them slightly less disruptive of incumbent pharmaceutical business models than autologous therapies [12]. However, allogeneic RM therapies are inherently disruptive of this centralizing trend because of the greater variability of biological inputs, creating technical difficulties in standardizing manufacturing and quality assurance and creating a need for close collaboration between therapy producers and clinicians (see ‘RM manufacturing processes’, ‘The links between manufacturing systems and distribution models’ and ‘Clinical adoption of autologous therapies’ sections). For these reasons, Harrison *et al.* foresee autologous therapies being manufactured in locally distributed,

‘near-hospital’ facilities [13]. This argument informs our focus on the nature and location of disruption in the development of RM therapies as it impacts on manufacturing, distribution and adoption in clinical settings.

Given the challenges of producing autologous cell therapies, decentralized or locally distributed manufacture is the only feasible approach for autologous and gene-based cell therapies. In response to BIS [9] and Abbasizadeh *et al.* [8], Harrison *et al.* [13] argue that, as a result of recent advances in technologies that facilitate “reproducible, repeatable and reliable manufacture of highly specialist products at a small scale” and real-time monitoring Quality Management Systems (QMSs), it is increasingly possible to move towards such locally distributed manufacturing models. They also claim that this small scale, locally distributed technology approach makes it possible to handle “inherently unstable personalized cell and gene therapies”.

Locally distributed manufacture of autologous cells will be an order of magnitude more disruptive of the existing pharmaceutical and biopharmaceutical business models than current manufacturing approaches to allogeneic therapies, hence the lack of interest in these therapies by these incumbent sectors. For allogeneic therapies, rather than adaptation of the existing big pharma business model there is a need to develop new business models and value chains, involving new start-up companies or existing companies moving into health care from other sectors of the economy (e.g., investment in manufacturing processes by Lonza and GE Healthcare).

The option for pharmaceutical companies to purchase locally distributed manufacturers of autologous cell therapies with a view to centralizing production does not exist, given the countervailing factors described above. Where such purchases have been attempted, cell therapy manufacturers have been frustrated by the lack of understanding of the acquiring firms about how RM works and how the feasible business models are different from the small or bio-molecule contexts investors are accustomed to. This is a common experience where incumbent large companies attempt to take on disruptive technologies. Given these constraints on investment the Advanced Therapies Manufacturing Action Plan [14] called for systemic investment in the sector to engender a more competitive fiscal environment.

Clinical adoption of allogeneic & autologous therapies

Manufacturing challenges are not the only factor limiting the development and hence the adoption of RM therapies. We previously noted a lack of co-operation between manufacturers and clinicians affecting the adoption of RM therapies [6], a view supported by Gardner *et al.* who observed that RM products will need to “work hard to create an adoption space” in current health-care settings [15].

Also, prevailing regulatory systems for RM therapies, along with other governance mechanisms such as the establishment of shared standards, have not been sufficiently adapted to meet the needs of centralized or locally distributed

manufacturing systems and personalized delivery to patients. RM therapies are also disruptive on current regulatory frameworks because of the introduction of methods beyond minimal manipulation and raw materials that are outside current supply chains for transfusion and transplantation. These questions are not dealt with here but have been addressed elsewhere [1]. Faulkner has also identified the challenges of “opposing forces for gatekeeping and innovation” by regulators of manufacturing and clinical practices [16]. We have also argued that accelerating clinical adoption is dependent on the creation of innovation ecosystems that promote rapid integration of RM and allied business models as well as creating an environment where new business models are given a chance to thrive [6,17]. We have previously argued that the public-private interaction by innovation broker institutions such as the Cell and Gene Therapy Catalyst are critical in the early phases of building supportive innovation ecosystems as they bridge value chain gaps, and de-risk early development stages [6]. This earlier work contributes to the frame described here to support analysis of the disruptive nature of RM therapies and the impact on: collaboration among clinicians, the clinical prescription system and hospital administrative systems; the viability of manufacturing processes; challenges related to ordering, storing and re-thawing therapies; and finally clinical adoption. We are aware that pricing and cost effectiveness are linked to manufacturing and clinical adoption, however we do not focus on them in this paper.

METHODOLOGY

We used the case study approach advocated by Yin for carrying out an empirical enquiry of issues that are embedded in real-life contexts [18]. In line with the argument by Stake we considered the complexity of the cases to understand the circumstances, contexts and other dynamics of the interactions of the organizations and actors we investigated [19]. We chose the case study approach because we were interested in the ‘how and why questions’ and the broader situational context within which these technologies are being developed.

Using a purposive sampling method, we approached 20 RM companies/organizations involved in RM-related activities in the UK and gained access to 10 of them. We conducted 18 semi-structured interviews (ten completed in 2014/15, with follow-up interviews in 2015/16). Semi-structured interviews allowed us the flexibility to follow themes and interesting leads that arose during the interview itself. After seeking informed consent, the interviews lasted between 1 and 2 hours and were audio-recorded and transcribed verbatim. Using manual thematic coding, we identified a number of salient themes, some of which are the focus of discussion in this paper. We used the STRATIS methodology to understand the business models, innovation ecosystems and value chains in the sector [20].

This paper also draws on our research on Proportionate and Adaptive Governance of Innovative Technologies [4], which has refined our thinking on the important features of, and differences between, disruptive and incremental innovations.

MANUFACTURING & CLINICAL ADOPTION OF RM THERAPIES: INTERVIEWEE PERSPECTIVES

Our analysis showed that allogeneic therapies are disruptive of many aspects of the business models of incumbent pharmaceutical firms, given the challenges involved in large scale manufacturing of cellular products, the storage and distribution of living materials, and delivery to very different markets. Large companies developing bio-pharmaceuticals will have overcome some, but not all of these disruptive challenges. Pharmaceutical companies’ adherence to current business models, despite these disruptive features of allogeneic therapies, have led them to persevere in developing large scale, centralized manufacturing facilities, designed to deliver a commoditized product internationally to large numbers of patients, in order to make RM therapies an attractive investment proposition. This has become the dominant expected future business model for RM therapies, in the process side-lining the development of autologous therapies, which are much less capable of achieving compatibility with the current business models of pharmaceutical companies.

The following sub-sections use our interview data to reflect on issues related to the disruptive nature of cell-based therapies.

Raw material sourcing

The challenge of inherent variability in living systems

A factor acknowledged in the literature, and confirmed by respondents

in all ten of our cases, is the complexity of working with raw materials composed of living systems which, unlike small molecules (Figure 1, left hand side), are difficult to standardize (Figure 1, right hand side). Specifically, the disruptive nature of RM first, emanates from these perspectives: RM raw materials cannot be subjected to traditional sterilization techniques and therefore need aseptic processing methods; second, because the therapy is integrated into the body unlike drugs which are metabolized and expelled, pharmacokinetics and pharmacodynamics are challenging; and third there is a need for defining, effecting and monitoring quality spanning the manufacturing and clinical phases. A respondent from a contract manufacturing organization reported that the private sector tends to play to its strengths by focusing on the “manufacturing piece because that’s closer to what a standard pharmaceutical company would do”, which covers raw material sourcing and processing. This implies that incumbent pharmaceutical companies, faced with a disruptive new technology, lock into what they already know and create an element of path dependency to make a disruptive transition more feasible. A disruptive element of the transition to RM for a conventional pharmaceutical company includes: incompatibility with chemical entities that can be easily standardized and produced in bulk and, because of chemical stability, intermediate and finished products can be stored for long periods with no need to identify the donor. Supporting these observations, he added:

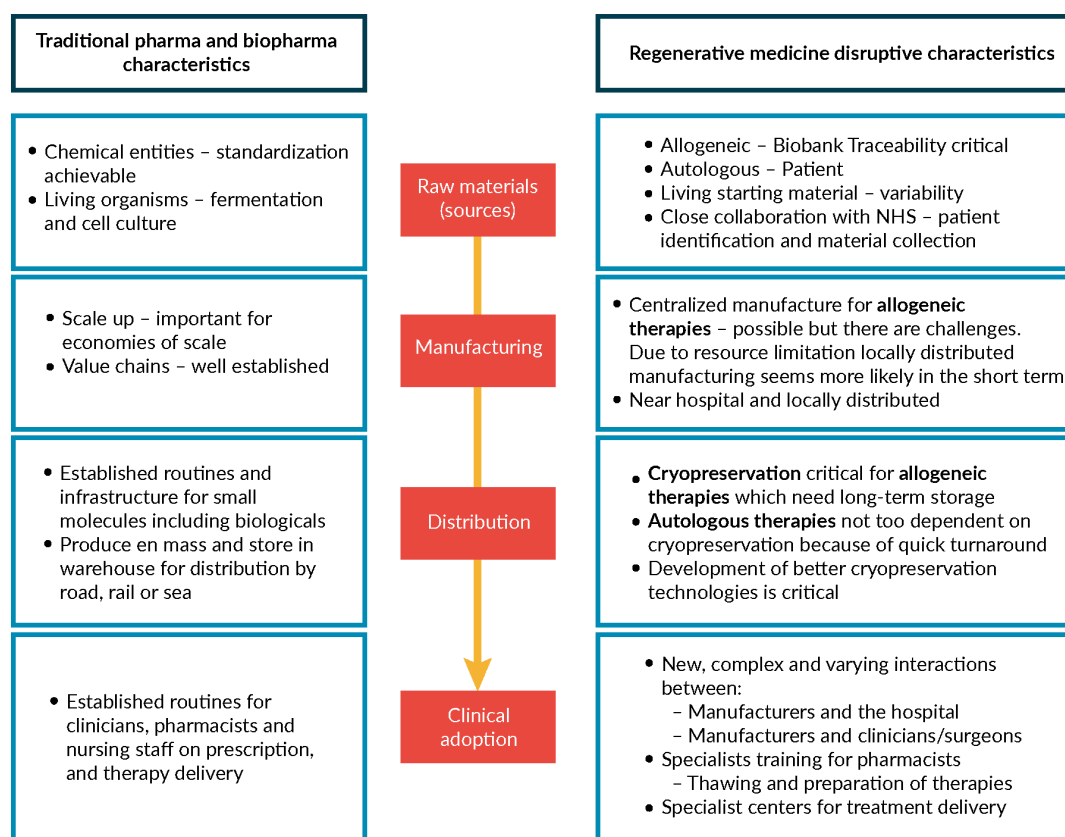
“Here you have a product which has been derived from

a human being, so it has all that ... inherent biological variability, or even [a cell] derived from me on two different occasions, it can behave in a different kind of way. The cell obviously is a living system in its own right ... it’s a living system in vitro and then it’s also a living system when you put it into the patient. So, like all living systems it has a nasty habit of doing its own thing.” – Managing Director, RM firm in research and development and contract manufacturing.

Other respondents acknowledged that they still do not fully understand the cell’s mechanism of action, having observed that cellular therapeutics work best when different types of cells are used in combination. So significant interactions between the different types of cell or tissue seem to be important for a functioning therapy. This is in contrast to small molecules and other biologicals where the biochemical pathways and pharmacokinetics end point are well known. Thus, for allogeneic therapies, innovators need to solve the challenge of standardizing and automating development processes for therapies with inherent variability, and to convince regulators of the robustness of their approach, especially for therapies that become integrated into the body. Furthermore, a product manufactured in the USA under FDA conditions cannot be assumed to be identical to a product manufactured in Europe under European cGMP conditions, according to respondents in our study. This creates manufacturing and regulatory

► FIGURE 1

The contexts where regenerative medicine is disruptive of incumbent manufacturing, distribution and clinical adoption systems.



compliance challenges for firms operating across geographical regions with different regulatory systems, for example Europe, Asia and the USA. This has implications for validation and quality assurance processes across different manufacturing facilities for the same firm, making centralized manufacturing more problematic, and forcing firms into locally decentralized or locally distributed manufacturing, illustrating the disruptive impact. Given that large scale manufacturing by the same firm across different countries needs to comply with different national regulatory requirements, it is difficult to move employees in regulatory interfacing jobs across

different countries, and it also multiplies the complement of regulatory personnel in the company compared to centralized manufacturing. This phenomenon affects both autologous and allogeneic therapies and impacts the whole process from donor selection to therapy delivery. Autologous therapies have an additional staffing burden where the manufacturing system is locally distributed.

The need for close collaboration between RM firms & the clinic

Another feature of the disruptive nature of RM development for

conventional drug production is the intricate collaboration required between manufacturers and, for example, the National Health Service (NHS) in the UK, for sourcing cells or tissue, and manufacturing (Figure 1 last box on the right). For a tissue regeneration case the respondent noted (Figure 3):

“...There is need in the UK to collaborate with the NHS for cadaver identification, followed by organ harvesting leading to transport of the organ to a specialist de-cellularization facility and adequate storage of frozen samples.” Respondent from a Tissue Regeneration Firm.

The NHS is critical for sourcing organs and, for some therapies, there is a need for the NHS to link up with manufacturers to collect cells from the patient for seeding a bio-matrix pre-surgery. This entails aligning work scheduling for

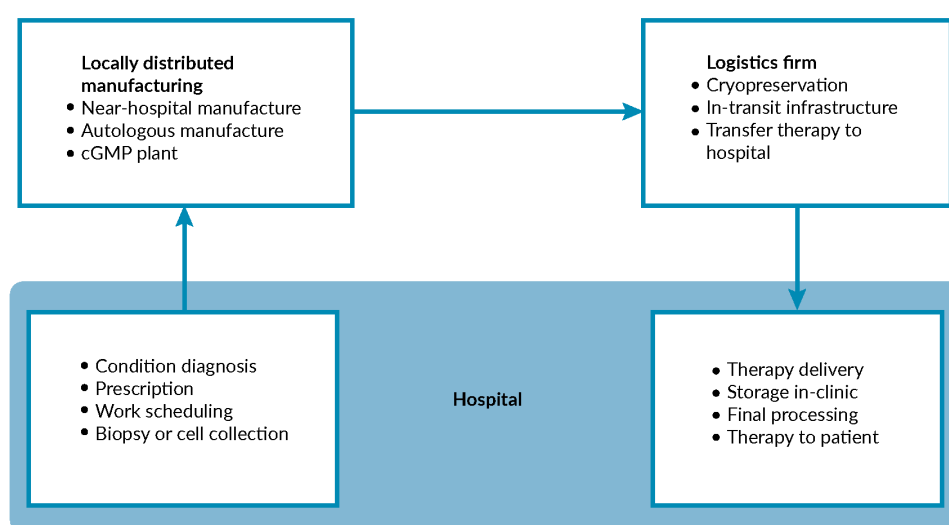
manufacturing with patients’ clinical visits. Such complex manufacturer-clinic interactions are an additional disruptive element beyond what is necessary for conventional drug or biopharmaceutical treatments. It requires RM firms to invest in specific RM technology delivery skills and training for pharmacists, specialist nursing staff, surgeons and technical/administrative supporting functions, including engineering and procurement. This also has important staffing and cost management implications for local NHS trusts, which are managed differently across the UK, affecting the ease of adoption into clinical practice.

RM manufacturing processes

Both allogeneic and autologous therapies are, or would be, disruptive of incumbent firms’ small

► **FIGURE 2**

The technical processes involved in clinical adoption of an autologous therapy such as CAR-T Cell.



molecule or biopharmaceutical companies on manufacturing processes, including the quality assurance techniques related to dealing with living cells which are inherently variable and difficult to standardize. However, allogeneic therapies can be scaled up (implying an incremental aspect), whereas autologous therapies cannot, although they can be scaled-out. The attraction of scale up, critical for building economies of scale for allogeneic therapies, is its similarity with manufacturing stages of conventional pharma business models, something investors in the sector are familiar with. A respondent from a firm specializing in allogeneic therapies reflected the scale up aspect as a key factor for their firm.

“... our [allogeneic] technology approach really gives us the ability to generate lots and lots of doses... And it makes an allogeneic approach, perhaps, more achievable.

Our cells are non-immunogenic, so they don't suffer the rejection problems that might be seen typically with an allogeneic approach.”
– Senior Executive for Cell Therapy Manufacturing Firm A.

For blood and tissue services, RM innovation is more incremental, as key processes such as raw material sourcing, manipulation and storage, and traceability requirements are already routine in the sector. However, there is lack of cross-sectoral knowledge about different therapy areas. Respondents in our study acknowledged that skills tend to be niche-focused and scarce in the

industry, especially in development and translational activities. This has implications for business continuity and the need for emerging firms to retain staff, especially given the close linkages between the firms and the NHS.

The need for co-evolution of technologies & innovations

For some allogeneic therapies involving for example gene therapy or immunotherapy, our study revealed the need for close interactions between therapy developers, technology suppliers and the clinic. The link between the technology supplier and the clinic is also required for locally distributed manufacturing systems or in/near-hospital manufacturing systems as part of the collaboration between the therapy developer and the NHS.

A key challenge raised for therapy developers was the need either to re-purpose existing technology or to design new technologies for manufacturing and quality assurance of therapies, as highlighted here:

“...when people are making ... protein therapeutics, which is the other large-scale culture technology, they don't want to keep the cells. They're deliberately breaking the cells up and trying to recover the protein out of them. We're doing exactly the opposite, we're trying not to damage the cells and get rid of everything else. So there is no technology out there at the moment that has been developed specifically for large scale cell recovery.”

– Senior Executive RM Collaborative Project

This firm was attempting to recover intact cells from culture, and there was no technology on the market at the time capable of that function. They reached out to their collaborators and their suppliers to design equipment capable of harvesting intact cells and considerable progress is now being made in this area, relevant to both autologous and allogeneic therapies [21]. This also happened for two other cases, where the in-house developers worked with their suppliers to design equipment for their manufacturing needs.

Respondents from organizations developing allogeneic therapies also acknowledged the need for closer interaction with the clinical setting for cell harvesting and therapy delivery and, by implication, the design and operability of technologies and operations used by the clinicians. An additional collaboration that emerged is the triad of therapy developers, contract manufacturers and technology developers, especially during therapy development optimization stages. The triad is important as technology optimization costs are borne by the therapy developer, which in most cases is resource constrained. Over time the triad is likely to morph into a dyad (therapy developer-contract manufacturer) especially in cases where a market authorized therapy is contract manufactured for the lead firm in another geographical location, in which case the contract manufacturer works closely with the clinical setting.

Challenge of specialized skills

A 2011 study by BIS highlighted the challenge bioprocessing units faced in recruiting and retaining skilled

staff for manufacturing, quality management, validation and batch release [9]. Our study confirmed these earlier findings, and our respondents reported that because of the niche focus of the technologies, training a person takes time and money, so it is important that those skills are retained.

The links between manufacturing systems & distribution models

Table 1 summarizes the expected manufacturing processes and likely distribution challenges faced by the ten cases we studied. At the time of the study none of the organizations had a market authorized product, and six therapy developers were at various stages of clinical testing.

Our study suggests that organizations are likely to favor centralized manufacturing for two reasons; skills shortages and infrastructure requirements for resource constrained SMEs that have to deal with infrastructural, technological, organizational, governance, value chain and regulatory hurdles when they are at a cash burn phase of development. Unless there are significant injections of cash, the locally distributed manufacturing approach may take time especially given the cost of setting up cGMP plants to manufacture clinical grade cell therapies. With dependence on central manufacturing come the challenges of cryopreservation and efficient distribution systems. Furthermore, this imposes an investment challenge for the clinic in terms of acquiring the cryopreservation infrastructure, and thawing therapies correctly just before use. These administrative and

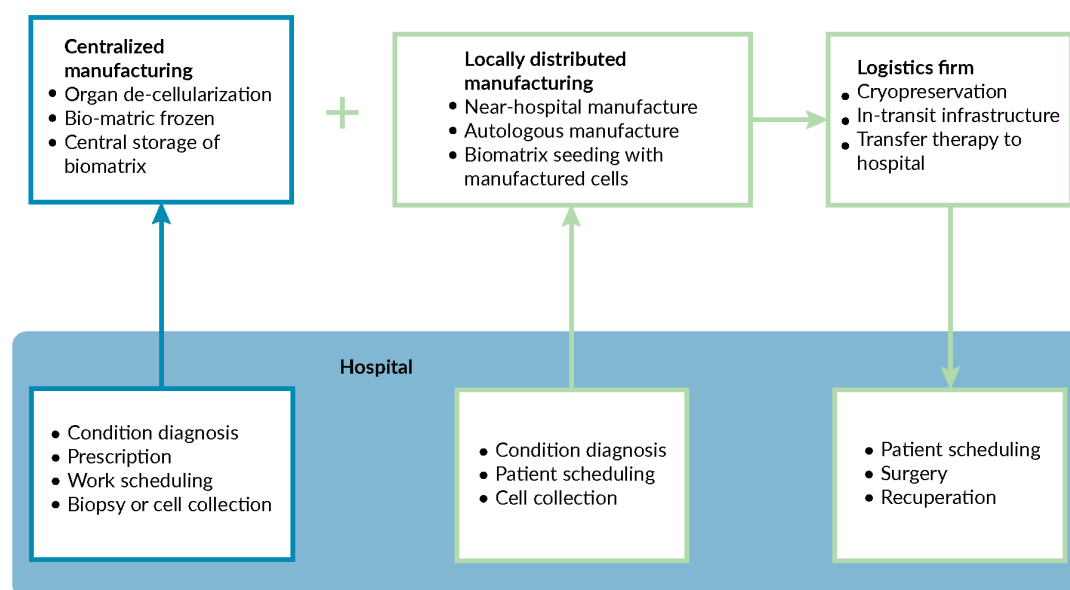
► **TABLE 1**

An analysis of the likely manufacturing process and anticipated distribution challenges for the ten cases investigated.

Case study	Therapy produced	Autologous – secondary business model	Manufacturing process	Distribution challenges
Contract manufacturer	Allogeneic – the main business model	Autologous – secondary business model	Centralized	Cryopreservation technology is important for extending shelf-life and therapy viability. For the clinic cost and management of cryopreservation equipment, and therapy handling
Blood and tissue; contract manufacture	Allogeneic – the main business model	Autologous – secondary business model		
Cell therapies	Allogeneic			
Cell therapies	Allogeneic			
Tissue regeneration	Biomatrix from cadaveric organ donations	Autologous	Locally distributed	Efficiently working with the NHS for identifying organ donors and acquiring viable tissue/organs on time
Immunotherapy – cancer		Autologous	Given that the companies are small and do not have resources to set up locally distributed manufacturing sites in the early days there will be specialist manufacturing centers where the company is sited	Requires efficient systems for cell collection and therapy delivery, whilst assuring therapy viability
Immunotherapy – cancer		Autologous	Centralized most likely	
Accelerated healing	Allogeneic			Requires efficient systems for cell collection and therapy delivery, whilst assuring therapy viability
Transfusion fluids	Allogeneic		Centralized or locally distributed if process automated	Similar to blood transfusion services

► **FIGURE 3**

The technical processes involved in tissue regeneration combining donated cadaveric organ and autologous cells delivered through surgery.



technological challenges are key impacts of innovative technologies especially on resource constrained SMEs with no prior interaction with the health system.

Clinical adoption of autologous therapies

In this section we present two examples: autologous immunotherapy (Figure 2) and autologous tissue engineering based on a donated cadaveric processed biomatrix, where therapy delivery involves surgery (Figure 3). We focus on the technical issues of therapy delivery, and not on re-imbursement, which others have already covered in some depth. Compared to incumbent biopharmaceutical and traditional pharma models of therapy delivery, there will need to be close linkages between the hospital, manufacturers, and logistics firms. Condition

diagnosis will not be different from current practice but an autologous therapy departs from conventional treatments in the prescription, requirement for work scheduling, and timing the collection of cells or biopsy with the work schedule in the cell manufacturing facility. The cell manufacturing plant also needs to align its production and delivery times with the time the patient has been booked to be at the hospital. Behind all these activities are numerous administrative tasks for the manufacturer, logistics firm and the hospital that are disruptive of the business model of a biotech or pharmaceutical firm. For blood transfusion services, already dealing with living materials, these logistic and administrative issues are closer to being incremental, although the challenges of clinical grade manufacturing of cells in bulk for therapy also include elements of disruption, albeit with a narrower gulf in skills

than for mainstream biotech and pharma companies.

Our second example, **Figure 3**, highlights the complex processes that need to be aligned when dealing with an organ transplant using autologous cells seeded on a donated organ. There would be a need to work closely with the NHS to identify organ donors and upon their death collect the organ while it is still viable. The organ would be processed to remove the cells of the donor and placed in cold storage. De-cellularization can be done in a centralized facility, as the organic matrix that will be obtained can be donated to any patient. For this part of the process the logistics and economies of scale suggest that a centralized manufacturing approach would be feasible. However, the autologous part of the process, collecting cells from the patient and growing them in a locally distributed manufacturing facility, presents the same challenges as discussed in 'The links between manufacturing systems and distribution models' section. In this case, the situation becomes more complicated because the seeded biomatrix is surgically inserted into the patient; increasing the number of actors that need to collaborate and align their processes in order to deliver tissue regeneration therapy.

Another interviewee reported that there is a need for co-evolution of processes, techniques and technologies between the clinical setting and the RM manufacturer, especially in the area of tissue regeneration as follows **[Figure 3]**:

"When a patient has been identified from the clinical setting, there is

cell-harvesting leading to cell culture/multiplication in a cGMP certified plant; re-cellularization of the matrix and surgery and recuperation of patient; all these activities need to co-evolve to allow adoption of an innovation."

– Founder of a Tissue Regeneration Firm

Particularly in the allogeneic cases we studied, shelf life was identified as a key component, and this is closely linked to cryopreservation technology which, as respondents reported, needs to be improved to ensure cell or tissue viability after storage for long periods. These aspects are important for effective handling of the pharmacy procedures in the hospitals.

DISCUSSION & CONCLUSIONS

We propose that understanding of the distinction between disruptive and incremental innovation, and of the nature, extent and location of the disruption across sectoral value chains, can help to guide company innovation strategies and government innovation support policies for RM, as already proposed for industrial biotechnology **[17]**. The RM-related disruption for pharmaceutical industry business models comes on top of an earlier phase of disruption caused by biopharmaceuticals (large protein molecules and monoclonal antibodies) that had already begun to re-shape the sector **[22–24]** and so to some extent paved the way for RM. However, RM imposes additional disruption on pharmaceutical and biopharmaceutical business

models to the extent that it has taken a decade of intensive intellectual and commercial investment to reach a stage where the small number of products that have been approved often under-perform and are withdrawn, and success is described narrowly in terms of the number of products in clinical trials [25]. Current analyses of the RM sector are still leading to calls for delivery systems designed for pills and biologics to be changed to accommodate cells [20].

Such difficulties and delays are more pronounced the more disruptive the technology is for the relevant sector. For RM therapies, faced with the individual disruptive elements described above, new value chains involving large companies that are new to the sector (e.g., Lonza, and GE Healthcare) and small innovative start-up companies are slowly beginning to emerge. Our analysis of the impacts of disruptive innovation includes the observation that innovation will proceed most rapidly and effectively if it is developed by the sector for which it is least disruptive and that, for life science innovation, government regulatory and policy decisions can make a transformative difference to the rapidity of uptake of a technology and the location of the innovation within an array of possible industry sectors [2].

The early regulatory choice to regulate stem cell therapies through the pharmaceutical regulatory system was one important factor driving the innovation trajectory for this technology towards the large scale, centralized manufacture of allogeneic therapies by incumbent pharmaceutical companies. These companies had an

interest in the technology and the commercial capability to support its development but the extent of disruption of their business models has been one factor slowing and in some cases stalling development of therapies. The converse of the focus on pharmaceutical companies has been the relative lack of private sector investment in the development of locally distributed manufacture of autologous therapies [1].

It is interesting to speculate on what the nature of current business models and value chains for RM therapies might have been, given a decision to regulate RM therapies as medical devices rather than drugs, or to focus more strongly on standards and less on regulation as the basis for ensuring safety, quality and efficacy [2]. Many of the disruption-related challenges would have been removed or diminished, but the necessary private sector investment may still have been lacking. Under these circumstances, the public sector and philanthropic organizations often step in to fill the gap in translational funding [18], but without commercially viable business models this is not a long-term stable solution.

With the publication of the White Paper on Regulation for the Fourth Industrial Revolution [26] the UK government is embarking on a new approach to the governance of innovative technologies. This could provide a route to adaptation of the innovation ecosystem for RM therapies that would enable the more rapid emergence of a broader array of innovative business models delivering a greater variety of therapies to meet complex patient needs [2].

The data/transcripts used in this study were archived with the ESRC under the following reference: Archive. 10.5255/UKDA-SN-852913

AUTHORSHIP & CONFLICT OF INTEREST

Contributions: All named authors take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

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